Discovering Treatments To Increase Learning and Memory for People With Down Syndrome

William Mobley
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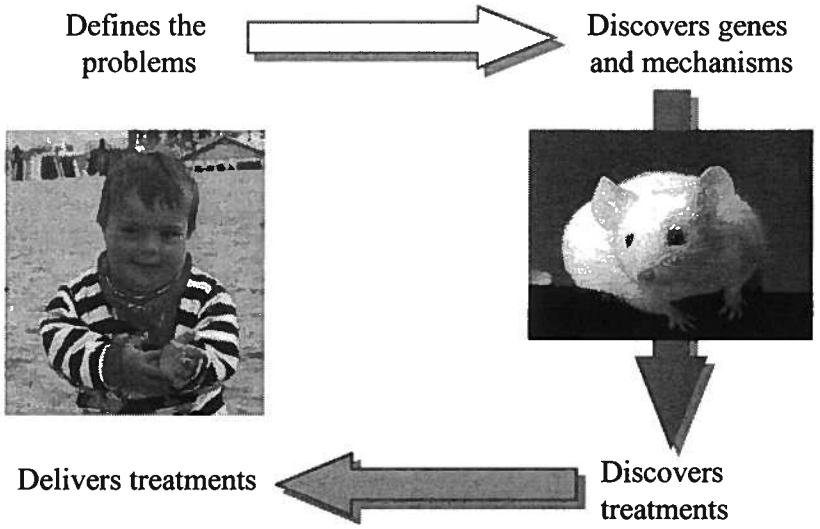
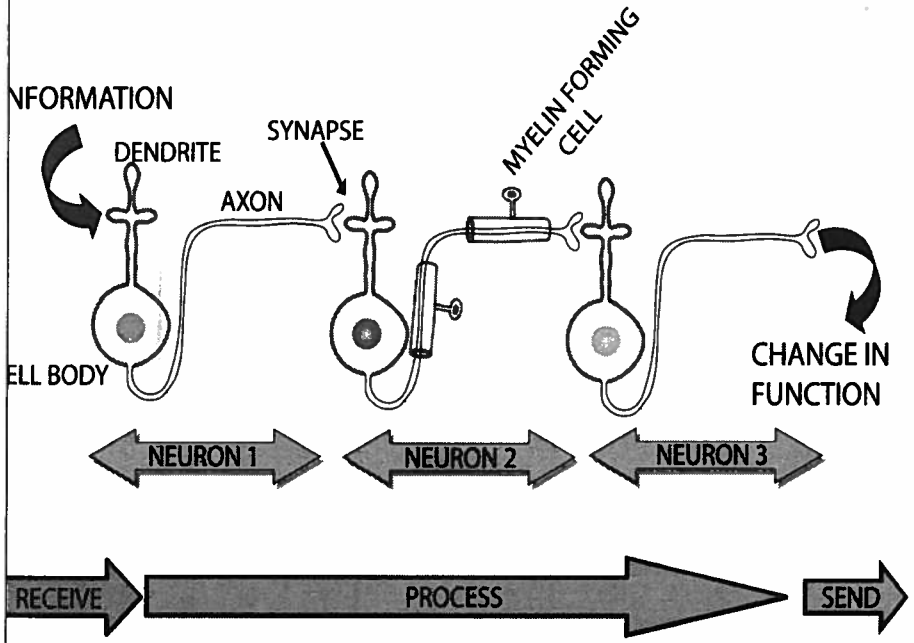
Center for Research and Treatment of Down Syndrome

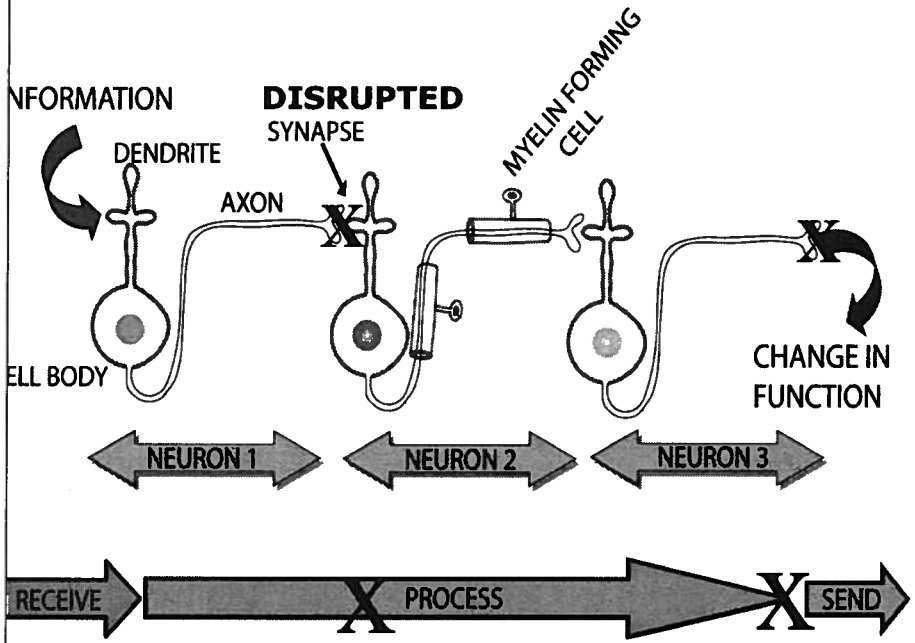
THE WORK OF THE CENTER



NEURONAL CIRCUITS MEDIATE ALL BRAIN FUNCTIONS



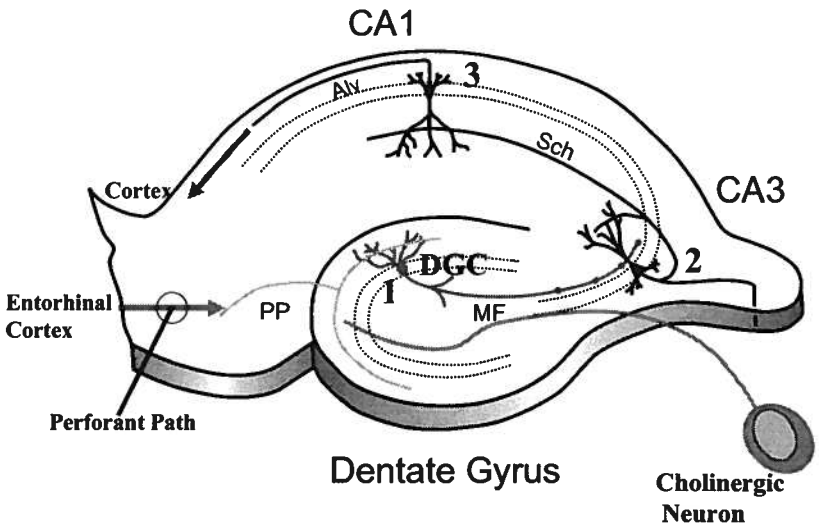
NEURONAL CIRCUITS ARE DISRUPTED IN DS



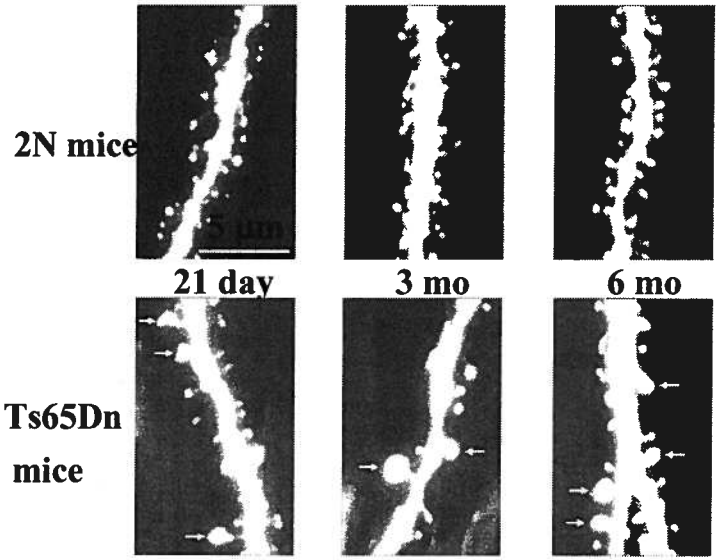
Neuronal Circuits Are Disrupted In Down Syndrome

- An imbalance in excitation and inhibition
- An imbalance in acid/base status
- Inadequate maintenance of circuits

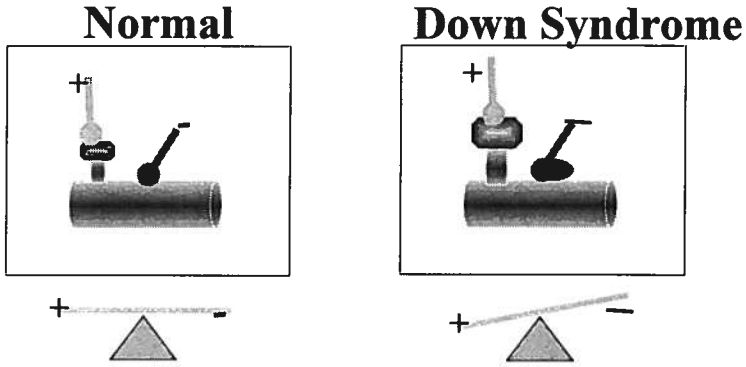
Anatomy of Hippocampal Circuits: a Brain Region Critical for Learning and Memory



Synapses Were Abnormal At All Ages: Decreased Density, Increased Size



Synapses Are Abnormal – But, Why?



Inhibition is Too Strong

Proposed Mechanism for Decreased Learning in Down Syndrome

Increased Inhibition

↓

Decreased Synaptic Plasticity

↓

Suppression of Learning

Proposed Treatment for Decreased Learning in Down Syndrome

Increased Inhibition

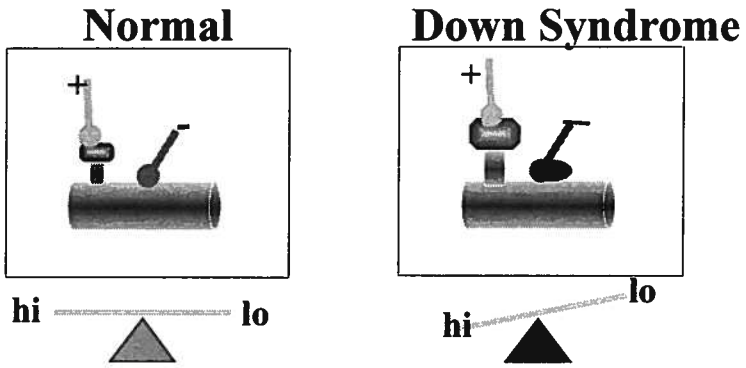
Decrease GIRK 2 ⊣ ↓ ⊣ **GABA B Antagonist**

Improved Synaptic Plasticity

↓

Improved Learning

Synapses Are Abnormal – But, Why?



The Brain Is Too Acidic

Proposed Treatment for Decreased Learning in Down Syndrome

Increased Acid

↓

Impaired Synaptic Plasticity

↓

Impaired Learning

Proposed Treatment for Decreased Learning in Down Syndrome

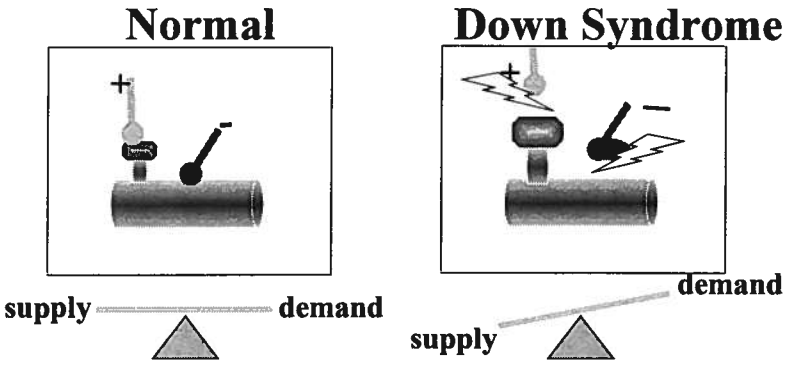
Increased Acid

⊣ Channel Antagonists

Improved Synaptic Plasticity

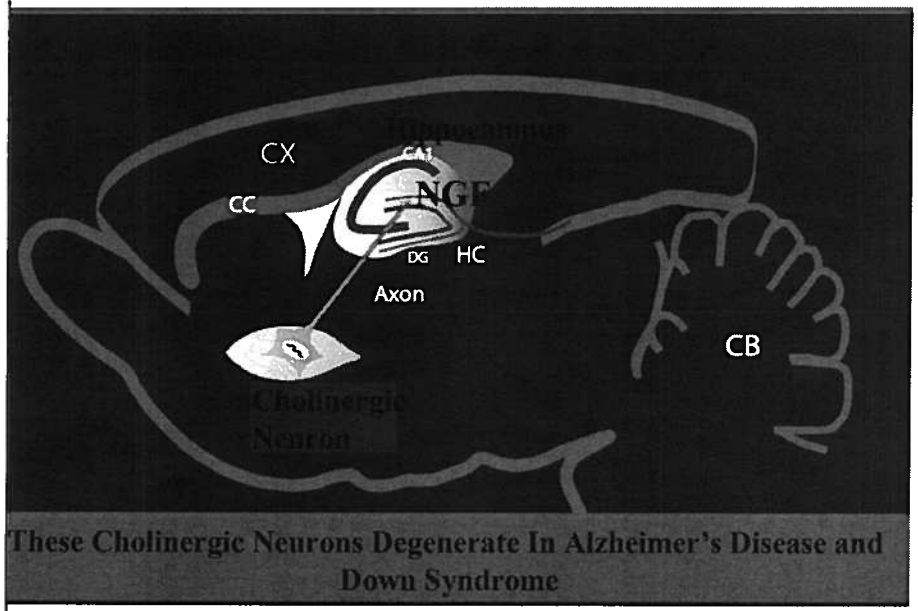
Improved Learning

Synapses Fail During Aging – Why?

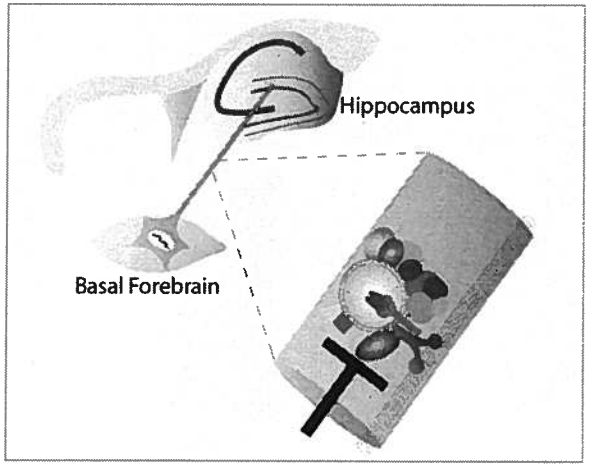


Decreased Growth Factor Support

Growth Factors Made in Hippocampus Regulate the Function and Survival of Cholinergic Neurons



An Extra Copy of App Causes Degeneration of Cholinergic Neurons



Proposed Mechanism for AD in Down Syndrome

Increased APP

↓

Decreased Synaptic Function

↓

Dementia

Proposed Treatment for Decreased Learning in Down Syndrome

Increased APP

↓ ⊣ Decrease APP

Improved Synaptic Function

↓

No Dementia

Convergence of Information

Genetic Studies → **Candidate Gene(s)/Mechanism** ← **Clinical Studies**, **Physiological Studies**

Candidate Gene(s)/Mechanism ↕ **Treatment**

DS Studies Now:

Fragmented, Underfunded, Ineffective

People

Congress

NIH Dir

NICHD **NIA** **NINDS** **NI__**

DS Studies Now: Fragmented, Underfunded, Ineffective

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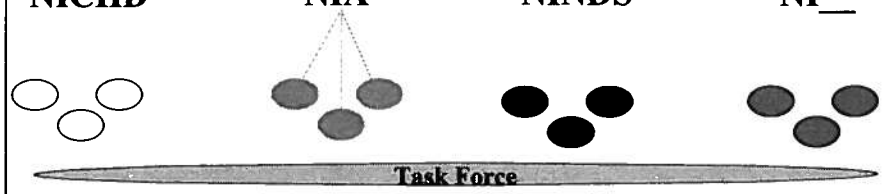


Existing Task Force – Good, But Doesn't Change the Game

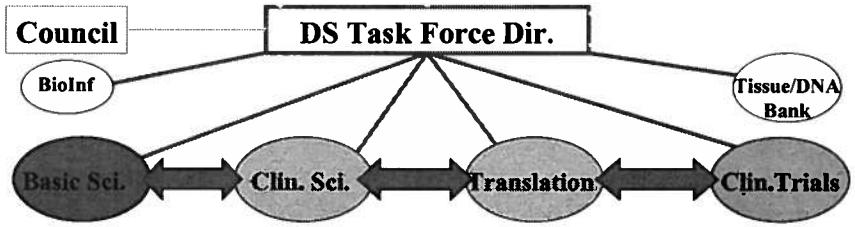
DS Studies Then: A New Task Force Changes the Game - Organized, Connected, Productive, Successful

People

Congress

NIH Dir.

NICHD NIA OPASI NINDS NI__



Why Make Down Syndrome A Priority? It Offers A Unique Opportunity To Enhance The Lives of Millions

- **All abnormalities in DS are due to an extra copy of a normal gene(s) on chromosome 21.**
- **It will be possible to define the genetic cause and mechanism for most or all abnormalities.**
- **It should be possible to treat most disorders in DS by reducing the action of a defined gene(s).**
- **Insights in DS will elucidate the cause of the same diseases in people who do not have DS.**

Understanding and treating DS will therefore help us care for millions of Americans without DS.

Many Diseases Are Linked to Down Syndrome: Studies of Down Syndrome Can Benefit Millions

- Mental Retardation - 100%
- Seizures – 10 to 15%
- Alzheimer's Disease- 100%

Cong. Heart Disease – 40%
Leukemia- ~10%
Diabetes, Type 1 – 5%
Celiac Disease – 20%
Infl. Bowel Disease – 0.4%
Thyroiditis – 50%
Psoriasis – 4%

Cancer (many solid tumors) – decreased
Atherosclerosis - decreased

We're not just asking what our country can do for people with Down syndrome,

Were asking what studies of people with Down syndrome can do for our country and the world